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PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES
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MEMORANDUM

SUBJECT

2,4-DICHLOROPHENOXYBUTYRIC ACID: Registrants Response to Justification for the High Dose Used in the Carcinogenicity Study.

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ACTION REQUESTED: Review registrant's response to deficiencies in 2,4-DB acid mouse carcinogenicity study and determine acceptability in fulfilling the Guideline requirement for a carcinogenicity study in mice [83-2b].

RESPONSE: The carcinogenicity study in mice [MRID No. 402575-01] was classified as supplementary due to a lack of justification for the highest dose tested in female mice [MRID No 419362-01; HED Doc.No.008813]. The information provided by the registrant in this submission, when taken together with the results of the 4-week range-finding and the carcinogenicity studies demonstrate that the highest dose tested was adequate to assess the carcinogenic potential of 2,4-DB acid.

Therefore, the carcinogenicity study in mice [MRID No. 402575-01] previously classified as Core Supplementary is upgraded to Minimum. This study satisfies the Guideline requirement 83-2(b) and is acceptable for regulatory purposes.



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I. BACKGROUND

In a 78-week carcinogenicity study, CD-1 mice were fed diets containing technical 2,4-dichlorobutyric acid at 0, 25, 250 or 750 ppm. The high incidence of mortality among males at 750 ppm which started about study Week 58 provided conclusive evidence that the highest dose tested was adequate to assess the carcinogenic potential of the test article in this sex. However, in females, the only significant change at this dose was an increase in mean kidney weights. Therefore, it was questioned whether the 750 ppm was an adequate dose for females. The original report stated that the dose levels for the carcinogenicity study were selected based on a 4-week range-finding study and that "the probable maximum tolerated dose for an oncogenicity study, based on increased liver weight, was less than 1000 ppm" [Vol I, p.14]. The study was classified as Supplementary pending justification for the 750 ppm dose used in female mice.

As per the Agency's request, the registrant provided a justification for the highest dose used for female mice. The registrant gave body weight data from the 4-week range-finding study but did not mention the increase in liver weights [MRID No. 419362-01]. Therefore, it was concluded that insufficient information has been given to justify 750 ppm as a MTD in females; the registrant should submit information - particularly relating to liver weight findings in the 4-week range-finding study - that more specifically address this point [Memo: B. Backus, HED to J. Coombs, RD, 10/17/91; HED Document No. 008813].

II. REGISTRANT'S RESPONSE

In response to the above request, the Registrant, in this submission, provided data on the liver weights from the 4-week study in which groups of 10 male and 10 female mice were fed 2,4-DB acid at 0, 30, 100, 300, 1000 or 3000 ppm for 28 days.

No changes in liver weights [absolute or relative] were seen in either sex at 30, 100 or 300 ppm. At 1000 ppm, both the absolute and the relative weights were slightly increased [not statistically significant] in males when compared to controls; relative weights were increased by 7% in this sex. In female mice, the absolute weights were slightly but not statistically significantly increased when compared to controls, whereas the relative liver weights [13%] were significantly [$p < 0.05$] increased [Table 1]. At 3000 ppm, both the absolute and relative liver weights were significantly increased in both sexes. However, early mortality precluded meaningful interpretation of the results.

In addition to the liver weights, at 1000 ppm the mean body weights were 9.5% lower in the males and 4% in the females while the mean body weight gains were lower by 17% in males and 15% in females as compared to controls. Decreases in body weights were seen in the absence of any alterations in food consumption indicating that the body weight loss was treatment related and not due to palatability problems. Therefore, the body weight effects seen in the range-finding study were also strong considerations in choosing the doses for the carcinogenicity study [Table 1]. The Registrant further stated that the lethality seen at 3000 ppm and decreased body weight gains in both sexes at 1000 ppm in the presence of normal food consumption after only 4 weeks, combined with decreased survival of males at 750 ppm in the carcinogenicity study, indicate that the dose of 750 ppm should be considered adequate both male and female mice.

III. REVIEW OF REGISTRANT'S RESPONSE

In the range-finding study, the NOEL was 100 ppm and the LOEL was 300 ppm; the LOEL was based on decreases in body weight gain in males [15%] and females [18%]. At 1000 ppm, treatment caused decreases in mean body weights and mean body weight gain [> 10%] in both sexes and increases in relative liver weights in females. The early mortality at 3000 ppm [in 9/10 males and 7/10 females by study week 2] preclude any meaningful interpretation of the results.

In the carcinogenicity study, 2,4-DB acid at 750 ppm caused a significant increase in mortality in males [all males sacrificed by Study Week 66] and increased relative kidney weights in females. No other treatment-related effects were observed and 2,4-DB acid did not induce neoplastic lesions in male or female mice.

It was concluded that the MTD was achieved or even exceeded in the males as evidenced by the life-threatening toxicity [i.e., early mortality] noted at 750 ppm in this sex. In the females, however, the minimal toxicity [i.e., increase in relative kidney weights] at 750 ppm suggests that a higher dose could have been used. However, a higher dose [1000 ppm] decreased body weight gain by > 10% and significantly increased relative liver weights only in females after 4-weeks of treatment. Consequently, it is possible that a higher dose might have led to early mortality in this sex also. Additionally, the LOEL of 300 ppm established in the range-finding study provides additional support to show that the 750 ppm dose was adequate. Therefore, the 750 ppm dose is considered adequate to assess the carcinogenic potential of 2,4-DB acid in both sexes of mice.

IV. CONCLUSION

The explanation provided by the registrant when taken together with the results of the 4-week range-finding and the carcinogenicity study demonstrate that the highest dose tested was adequate to assess the carcinogenic potential of 2,4-DB acid in both sexes of mice.

Therefore, the carcinogenicity study in mice, previously classified as **Supplementary** is upgraded to **Minimum**. This study satisfies the Guideline requirement 83-2(b) and is acceptable for regulatory purposes.

Table 1. Changes in Body Weight and Liver Weights in Mice Fed 2,4-DB for 4-Weeks.

Body Weight Gain [(G) And Percent Difference from Controls].

10/sex/Group	0 ppm	30 ppm	100 ppm	300 ppm	1000 ppm
Males	9.9	9.5	9.3 [-6%]	8.4 [-15%]	8.2 [-17%]
Females	5.4	6.2	5.3	4.4 [-18%]	4.6 [-15%]

Mean Absolute Liver Weights (g).

10/sex/Group	0 ppm	30 ppm	100 ppm	300 ppm	1000 ppm
Males	1.3 ± 0.13	1.3 ± 0.12	1.3 ± 0.11	1.3 ± 0.09	1.4 ± 0.14
Females	1.0 ± 0.10	1.1 ± 0.18	1.1 ± 0.88	1.1 ± 0.13	1.2 ± 0.12

Mean Relative Liver Weights (g).

10/sex/Group	0 ppm	30 ppm	100 ppm	300 ppm	1000 ppm
Males	5.14±0.28	4.98±0.28	4.93±0.38	5.11±0.42	5.49±0.32
Females	5.03±0.26	5.08±0.36	5.31±0.39	5.21±0.45	5.70±0.21*



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